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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,718	07/09/2003	Herman Waldmann	695458-79	9454

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EXAMINER

BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

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01/29/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/615,718	Applicant(s) WALDMANN ET AL.	
	Examiner David J. Blanchard	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 October 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-10 and 12-17 is/are pending in the application.
- 4a) Of the above claim(s) 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6-10,12-15 and 17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 October 2007 has been entered.
2. Claims 2-5 and 11 are cancelled.
3. Claim 16 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.
4. Claims 1, 6-10, 12-15 and 17 are under consideration.
5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Maintained

6. The objection to the disclosure as containing sequences that are encompassed by the sequences rules (37 C.F.R. §§ 1.821-1.825) and require sequence identifiers is maintained.

The response filed 10/29/2007 still does not address this requirement to comply with the sequence rules and as such the objection is maintained for reasons already of record (e.g., see item nos. 6-8 of the Office Action mailed 8/4/2006).

7. The rejection of claims 1, 6-10, 12-15 and 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claims contain subject matter, which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 10/29/2007 submits the same arguments filed previously (2/1/2007), stating that antibodies and peptides are known to those skilled in the art, and one skilled in the art can modify the antibody with a peptide by techniques that are known to those skilled in the art. According to applicant, once one skilled in the art modified the antibody with a peptide, one skilled in the art also would be able to determine, by techniques known to those skilled in the art, whether binding of the modified antibody to the therapeutic target had been reduced vis-à-vis the unmodified antibody. Applicant has shown, as acknowledged by the examiner, that one may modify the CAMPATH-1H antibody with the CD52 mimotope QTSSPSAD or QTSAAVD and one skilled in the art would understand that other antibodies may be modified with peptides in a similar manner. Applicants' arguments have been fully considered but are not found persuasive for the reasons already of record and reiterated herein for convenience. It is reiterated that the claims are drawn to a pharmaceutical comprising a therapeutic antibody being modified with a peptide that reduces binding of the antibody to the therapeutic target and is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target. Thus, the claims encompass an extremely large genus of therapeutic antibodies linked to a genus of peptides, disclosed for treating, preventing and/or reducing any disease condition or disorder. However, written description of the present application only reasonably conveys a therapeutic humanized anti-CD52 antibody, CAMPATH-1H, modified by linking two different peptides, CD52 mimotope (QTSSPSAD) or CD52 mimotope mutant 9 (QTSAAVD) in which the antibody-mimotope conjugate reduced the immune response (i.e., cytokine release) and had a therapeutic effect by binding CD52. Applicants' reliance on the description of a single species of humanized anti-CD52 antibody, CAMPATH-1H, modified by linking a CD52 mimotope (QTSSPSAD or QTSAAVD) and having the properties and characteristics unique to the CAMPATH-1H-CD52 mimotope (QTSSPSAD or QTSAAVD) interaction is not representative of the entire genus because the genus is highly variable, inclusive

to a variety of therapeutic antibodies, having different therapeutic targets, functions and effects (i.e., agonistic, antagonistic, blocking, recruitment of effector cells, ect) and which are linked to any peptide, inclusive to peptides of varying lengths and chemical composition. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). The specification provides no other structural description of a therapeutic antibody being modified with a peptide that reduces binding of the therapeutic antibody to a therapeutic target, wherein the therapeutic antibody-peptide pair is effective for reducing an immune response against the antibody and produces a therapeutic effect by binding to the therapeutic target, other than the ones specifically exemplified; in essence the specification simply directs those skilled in the art to go figure out for themselves what the claimed genus of therapeutic antibody-peptide pairs look like. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, Applicants' argument that therapeutic antibodies and peptides are known to those skilled in the art and one skilled in the art also would be able to determine, by techniques known to those skilled in the art, whether binding of the modified antibody to the therapeutic target had been reduced vis-à-vis the unmodified antibody seems to go more toward enablement than description. That is, the argument seems intended to show that, following the teachings in the specification, those skilled in the art could have produced other therapeutic antibody-peptide pairs, and determined which (if any) would have the claimed properties, without undue experimentation. The instant rejection is based on lack of adequate written description, not lack of enablement. The written

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description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed CAMPATH-1H-mimotope species. Therefore, only the humanized anti-CD52 antibody, CAMPATH-1H, linked to the CD52 mimotope QTSSPSAD or QTSAAVD, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph and the rejection is maintained.

8. The rejection of claims 1, 6-10, 12-15 and 17 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising CAMPATH-1H (humanized anti-CD52 antibody), modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAVD, does not reasonably provide enablement for all other therapeutic proteins and therapeutic antibodies modified (i.e., bound or linked) with just any other peptide or molecule (i.e., compound), wherein the therapeutic protein or therapeutic antibody has reduced side effects and produces a therapeutic effect by binding to the therapeutic target is maintained.

The response filed 10/29/2007 submits the same arguments filed previously (2/1/2007), which state that as noted above (description requirement) that applicants'

have modified the CAMPATH-1H antibody with two different mimotope peptides and once applicants' had proven the principle with the CAMPATH-1H antibody, one skilled in the art would know readily how to modify other antibodies with other peptides to reduce the binding of such antibodies to a therapeutic target. Applicant states that because applicants' have proven the principle with respect to the CAMPATH-1H antibody bound to two different mimotopes, one skilled in the art would reasonably expect that other antibodies can be modified with other peptides to reduce binding of such antibodies to their respective therapeutic targets. Applicant asserts that the examiner has provided nothing other than sheer speculation in an attempt to show otherwise and the art cited by the examiner showing that protein chemistry is unpredictable is nothing more than a "red herring" and have no relevance to whether the claims are enabled. Applicants' arguments have been fully considered but are not found persuasive for reasons already of record and reiterated herein for convenience. Again, while applicant has proven the principle that the CAMPATH-1H antibody modified with the CD52 mimotope QTSSPSAD or QTSAAVD, reduces binding of CAMPATH-1H to CD52, reduces an immune response against the antibody and produces a therapeutic effect by binding to the therapeutic target CD52, applicant has not proven that the same principle is extendable to the broad scope of the claimed genus of therapeutic antibodies and peptide pairs, wherein the just any peptide reduces binding of a therapeutic antibody to a therapeutic target, reduces an immune response against the therapeutic antibody and produces a therapeutic effect by binding to the therapeutic target. Applicants' argument that the skilled artisan could modify other antibodies with other peptides to reduce the binding of such antibodies to a therapeutic target is not persuasive because the issue is make and use, not make and test to see if the skilled artisan could use. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical

elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03. The "principle" upon which applicant relies is limited to a humanized anti-CD52 antibody (CAMPATH-1H) linked to a CD52 mimotope (i.e., QTSSPSAD or QTSAAVD), which reduces binding to CD52, but is competitively displaced by CD52 *in vivo* due to more favorable association and dissociation binding kinetics and the CAMPATH-1H-mimotope conjugate reduces cytokine release. However, the art points out that even minor changes in an epitope sequence may dramatically effect the antigen-binding function of an antibody. Lederman et al (Molecular Immunology 28:1171-1181, 1991, cited on PTO-892 mailed 8/4/06) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980, cited on PTO-892 mailed 8/4/06) disclose the dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Therefore, even one amino acid difference in the peptide used for the modification of the therapeutic antibody could dramatically change the affinity or binding to the antibody combining site. Thus, applicants' 'proof of concept', which is specific to the unique binding properties of the CAMPATH-1H antibody and CD52 function, could not be predictably extrapolated by those skilled in the art to the genus of peptides for modifying the genus of therapeutic antibodies or even for a particular therapeutic antibody. Applicant has not provided any guidance or direction as to how the properties of the CAMPATH-1H-CD52 mimotope interaction are predictive of the interaction between a particular therapeutic antibody and a given peptide sequence, such that the peptide modifies the therapeutic antibody to reduce binding to the therapeutic target, reduces an immune response against the therapeutic antibody and produces a therapeutic effect by binding to the therapeutic target. There is insufficient evidence or nexus between the properties of the CAMPATH-1H-CD52 mimotope interaction and making and using any other therapeutic antibody bound to just any peptide that inhibits binding of the therapeutic antibody to the therapeutic

target, reduces an immune response against the therapeutic antibody, and wherein the antibody produces a therapeutic effect by binding to the therapeutic target.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Thus, rather than rely on sheer speculation or create some fallacy by presenting an irrelevant topic in order to divert applicants' attention from the present enablement issue, the examiner has provided documentary evidence directly related the enablement issue in the present application given the broad scope of the claims at issue, directed to any therapeutic antibody modified with just any peptide and having the claimed features. As stated in the MPEP: once the examiner has advanced a reasonable basis for questioning the adequacy of the disclosure, it becomes incumbent on the applicant to rebut that challenge and factually demonstrate that his/her application disclosure is in fact sufficient (MPEP 2164.05). It should be noted also that it is not opinion evidence directed to the ultimate legal question of enablement, but rather factual evidence directed to the amount of time and effort and level of knowledge required for the practice of the invention from the disclosure alone which can be expected to rebut a prima facie case of nonenablement. See *Hirschfield*, 462 F. Supp. at 143, 200 USPQ at 281. Therefore, the burden is upon the Applicants' to show objective evidence for other members of the genus of a therapeutic antibody modified by a peptide that reduces binding to a therapeutic target, reduces an immune response against the antibody and produces a therapeutic effect by binding to the therapeutic target.

In view of the broad scope of the claims at issue, the lack of the predictability of the art to which the invention pertains as evidenced by Lederman et al and Li et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed pharmaceutical comprising a therapeutic antibody bound or linked to a peptide that inhibits binding of the therapeutic antibody to the therapeutic target, reduces an immune response against the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the

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claimed pharmaceutical and absent working examples providing evidence which is reasonably predictive that the claimed pharmaceutical comprising a therapeutic antibody bound or linked to a peptide inhibits binding of the therapeutic antibody to the therapeutic target, reduces an immune response against the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target, commensurate in scope with the claimed invention.

For these reasons and those already of record the rejection is maintained.

9. The rejection of claims 1, 6, 9-10 and 17 under 35 U.S.C. 102(b) as being anticipated by Hale G (Immunotechnology, 1:175-187, 1995, cited on PTO-892 mailed 8/4/2006) is maintained.

The response filed 10/29/2007 again states that the present invention is directed to a pharmaceutical comprising a therapeutic antibody that binds to a therapeutic target, wherein the therapeutic antibody is modified with a peptide that inhibits binding of the antibody to the therapeutic target and is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target. Applicant acknowledges that Hale discloses the binding of CAMPATH antibodies to mimotopes of the CD52 antigen, however, applicant again argues that the purposes of the binding studies disclosed in Hale were to characterize the CD52 epitope bound by CAMPATH more precisely, and to construct analogues of such epitope that would be useful in assays and for purifying CAMPATH antibodies, as well as studies for the antigen-binding site. Further, Applicant states that Hale is directed solely to studying the binding of CAMPATH antibodies to CD52 mimotopes in order to aid in the development of assays, of methods of purifying CAMPATH antibodies, and in studying the antibody-antigen interaction between CAMPATH antibodies and the CD52 antigen or mimotopes thereof. Applicants' arguments have been fully considered but are not found persuasive. It is reiterated that the fact that Hale was concerned with a different purpose or doesn't recognize that the CAMPATH-1H humanized antibody

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bound to the synthetic peptide, QTSSPSAD, is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target, does not distinguish the claimed pharmaceutical comprising a therapeutic antibody bound to a peptide that inhibits binding of the antibody to a therapeutic target, from the anti-CD52 humanized antibody, CAMPATH-1H, reversibly bound by the synthetic peptide, QTSSPSAD, a CD52 mimotope that inhibits binding of CAMPATH-1H to human lymphocytes expressing CD52 (i.e., "therapeutic target") by about four fold and the antibody is disclosed in various buffers including buffered saline (PBS) (i.e., reasonably interpreted to be a "pharmaceutically acceptable carrier") as taught by Hale. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. V. IRECO, Inc* 51 USPQ2d 1943 (Fed. Cir. 1999). Applicant is reminded that the intended use of the modified antibody "for reducing an immune response", "for producing a therapeutic effect by binding to the therapeutic target" are given no patentable weight (see MPEP 2111.02).

For these reasons and those already of record, the rejection is maintained.

10. Then provisional rejection of claims 1, 6-10, 12-15 and 17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-41 of copending Application No. 09/979,948 is maintained.

The response filed 10/29/2007 advises the examiner that Application Serial No. 09/979,948 is still pending. The examiner acknowledges applicants' advice, however, the claims in the instant application are not currently in condition for allowance, no terminal disclaimer has been filed and the conflicting claims remain drawn to patentably indistinct inventions and hence, the rejection is maintained. With respect to the present provisional obviousness-type double patenting rejection and the fact that Application

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Serial No. 09/979,948 is still pending , Applicant is reminded that MPEP 804(I)(B)(1), which states:

"If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn."

11. The rejection of claims 1, 6-10, 12-15 and 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained.

The response filed 10/29/2007 does not address this rejection and as such the rejection is maintained for reasons already of record (e.g., see item no. 20 of the previous Office Action mailed 4/19/2007)

12. No claim is allowed.

13. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643